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09/493,211	01/28/2000	Philip Richard Abraham	Q57666	1944

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EXAMINER

KAM, CHIH MIN

ART UNIT PAPER NUMBER

1653

DATE MAILED: 04/09/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/493,211

Applicant(s)

APPELMELK ET AL.

Examiner

Chih-Min Kam

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-47 is/are pending in the application.
- 4a) Of the above claim(s) 14 and 31-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13, 15-30 and 40-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Status of the Claims

1. Claims 1-47 are pending.

Applicants' amendment and declaration of Dr. Philip Richard Abraham filed on January 16, 2002 (Paper Nos. 14 and 15, respectively) are acknowledged, and applicants' response has been fully considered. Claims 1-6, 8-15, 21-23 and 28-29 have been amended, claims 14 and 31-39 stand withdrawn, and new claims 40-47 have been added. Thus, claims 1-13, 15-30 and 40-47 are under examination.

2. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. Please use bracket ([]) to indicate the deletion in the amended claim.

Objection Withdrawn

3. The previous objection to claims 8-12 regarding "SEQ ID NO:", is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 8 in Paper No. 14.

Rejection Withdrawn

Claim Rejections - 35 USC § 101

4. The previous rejection of claim 1, under 35 U.S.C.101, regarding the claimed invention being directed to non-statutory subject matter, is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 8 in Paper No. 14.

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Claim Rejections - 35 USC § 112

5. The previous rejection of claims 1-7, 13 and 15-30, under 35 U.S.C.112, first paragraph, is withdrawn in view of declaration of Dr. Philip Richard Abraham (Paper No. 15), and applicants' response at pages 8-11 in Paper No. 14.

Declaration of Philip Richard Abraham, one of the three inventors, has been fully considered. In the Declaration, pages one and two state the education background and academic career of Philip Richard Abraham; Pages 2-6 state each peptide of formula (1) in the claims forms an α -helix. In particular, Dr. Abraham indicates the EP peptide (Gly-Arg-Tyr-Arg-Ile-Tyr-Arg-Arg-Ile-Tyr-Arg-Arg-Tyr-Ile-Arg-Ile-Ile-Ile-Gly) has an α -helix structure, which is predicted from a number of currently acceptable methods for peptide modeling (Exhibits 1-3), rather than a β -sheet structure as indicated by Examiner in the previous Office Action. He further asserts BP2 peptide and any peptide within the definition of the claim (i.e., R^1 - R^2 -A-B-(A-B-C-A)_m-(C)_n- R^3) are amphipathic, cationic and form stable α -helix; Pages 6-10 state due to the shared characteristics of the peptides of the consensus formula, and the results with the experimental peptides reported in the specification, the skilled artisan would expect that each of the peptides of the consensus formula function for the purposes recited in the claims. He further asserts that additional experimental evidence in mice (Exhibits 7-10) demonstrating the peptides of the consensus formula can be used for the treatment of infection by bacteria, inflammation or septic shock and as prophylactic as recited in the claims; Pages 10-12 state each peptide encompassed by the consensus formula is effective in the treatment of humans. He indicates murine models of human illness are now commonly accepted, and the results from testing in mice are often directly applicable to humans. He further provides the data indicating antibiotic

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properties of BP2 in human whole blood (Exhibit 11) and concludes the peptides of the claimed invention have a therapeutic potential in treating human infectious disease. The declaration of Philip Richard Abraham is found persuasive, thus the rejection under 35 U.S.C.112, first paragraph, is withdrawn.

6. The previous rejection of claims 5, 15, 21, 22, 23, 28-30 and 44 under 35 U.S.C.112, second paragraph, regarding the term “one or more of the sequence motifs (A-B-C-A)”, “R¹-R² and R³ each have a number of amino acids ranging from 0 to 15”, “and/or”, “a non-peptide carrier, tag or label”, “derivatives and analogues”, “such as”, “has or can have occurred”, or “a mixture of at least two peptides according to claim 1”, or, the lack of method steps in treatment of microbial infection, is withdrawn in view of applicants’ amendment to the claim, and applicants’ response at pages 12-16 in Paper No. 14.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 8-12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a peptide, BP1, BP2, BP2.3, BP2.4, or BP2.5. As written, the claim does not explicitly indicate the hand of man. Insertion of “purified” in connection with a peptide is suggested. See MPEP § 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

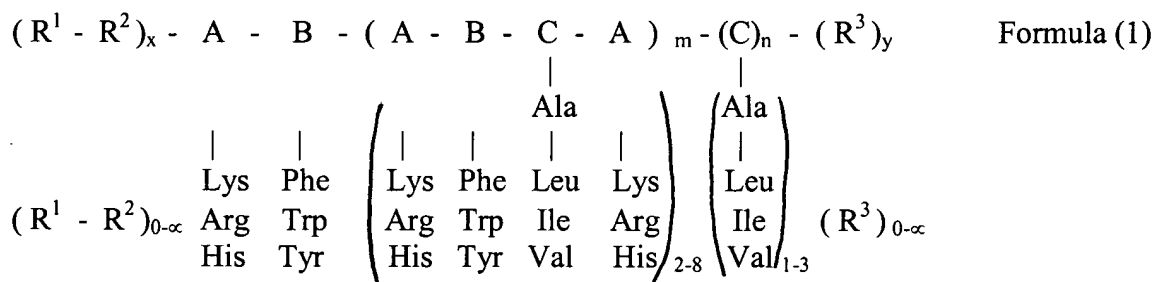
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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8. Claims 1-13, 15-30 and 40-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

From applicants' response, it appears that the previous rejection under 35 U.S.C. 112, second paragraph, should have provided a more detailed explanation. Formula (1) is not reflected in the written part of claim 1 describing the formula, nor are the dependent claims consistent with the formula (1). Furthermore, comparison of the amino acid sequences of BP1, BP-2, BP2.3, BP2.4 and BP2.5 does not conform to formula (1).

Below is a written survey of formula (1), wherein the amino acid options for each variable A, B, C are set forth below each letter. For numeric values of x, m, n and y are set forth as well. R¹, R² and R³ are understood to be any amino acid. It is understood by all artisan that the variables within parentheses are repeated the proscribed numeric value subscript at the second or outer parentheses.



Therefore, in accordance to the formula (1), and inserting the amino acid required by lettered variables, a sequence describing formula (1) can be written as follows:

(Gly-Ser)₂-Arg-Tyr-(Lys-Phe-Leu-His)₂-(Leu)₃-(Thr)₄ or, more specifically,
Gly-Ser-Gly-Ser-Arg-Tyr-Lys-Phe-Leu-His-Lys-Phe-Leu-His-Leu-Leu-Leu-Thr-Thr-Thr-Thr.

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It appears that applicants intend each series of amino acid described in each parenthesis to be independent, that is that the parenthesis (A-B-C-A)₂ can be 8 wholly different amino acid instead of a repeat of 4 specific amino acid. This is considered to be repugnant use of art-recognized formula construction. If applicants intend that the 4 amino acid sequence does not have to be specifically repeated, the additional sequences presented in parentheses should be placed in the formula (1).

Below are the BP1, BP-2, BP2.3, BP2.4 and BP2.5 sequences and how these sequences may fit into a formula similar to formula (1). As noted in claim 1, the variables in (A-B-C-A) can be reversed as (A-C-B-A). However, the formula as written does not reflect including this desired sequence. Therefore, because R¹ is "an amino acid", the limitation of claim 4 that it is multiple amino acids does not find antecedent basis in formula (1).

BP1 Gly-Arg-Leu-Arg-Lys-Lys-Trp-Lys-Ala-Phe-Lys-Lys-Phe-Leu-Lys-Ile-Leu-Ala-Cys

$$(R^1-R^2)_{x=0} \quad \begin{array}{c} | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \\ A - B - (A - C - B - A) - (A - B - C - A) - C \end{array} (R^3)_{y=1}$$

BP2 Gly-Lys-Trp-Lys-Leu-Phe-Lys-Lys-Ala-Phe-Lys-Lys-Phe-Leu-Lys-Ile-Leu-Ala-Cys

$$\begin{array}{c} | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \\ A - B - (A - C - B - A) - (A - C - B - A) - (A - B - C - A) - C \end{array} (R^3)_{y=1}$$

 Where $(R^1-R^2)_{x=0}$

BP2.3 Gly-Lys-Trp-Lys-Ala-Phe-Lys-Lys-Ala-Phe-Lys-Lys-Phe-Ala-Lys-Ile-Leu-Ala-Gly

$$\begin{array}{c} | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \\ A - B - (A - C - B - A) - (A - C - B - A) - (A - B - C - A) - C \end{array} (R^3)_{y=1}$$

 Where $(R^1-R^2)_{x=0}$

BP2.4 Gly-Lys-Trp-Lys-Leu-Phe-Lys-Lys-Ala-Phe-Lys-Lys-Phe-Leu-Lys-Ile-Leu-Ala-Gly

$$\begin{array}{c} | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \\ A - B - (A - C - B - A) - (A - C - B - A) - (A - B - C - A) - C \end{array} (R^3)_{y=1}$$

 Where $(R^1-R^2)_{x=0}$

BP2.5 Cys-(Gly)₉-Lys-Trp-Lys-Ala-Phe-Lys-Lys-Ala-Phe-Lys-Lys-Phe-Ala-Lys-Ile-Leu-Ala-
 Cys-Gly
$$\begin{array}{c} | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \\ A - B - (A - C - B - A) - (A - C - B - A) - (A - B - C - A) - C \end{array} (R^3)_{y=1}$$

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Where Cys-(Gly)₉ does not fit to (R¹-R²)_x

9. Claims 1-7, 13, 15-30 and 40-47 are indefinite because of the use of the term “R¹, R² and R³ each are an amino acid, x is an integer ≥ 0 , y is an integer ≥ 0 ” or “may have the retro orientation (A-C-B-A)”. The term “R¹, R² and R³ each are an amino acid, x is an integer ≥ 0 , y is an integer ≥ 0 ” or “may have the retro orientation (A-C-B-A)” renders the claim indefinite, it is unclear in the claim what peptide is intended for the formula (1), e.g., which amino acid is used for R¹, R² and R³, how many R¹, R² and R³ are included in the formula (1), and what amino acid sequence the peptide of formula (1) has; whether the formula (1) has the retro orientation (A-C-B-A) or not as to “may have”. Claims 2-7, 13, 15-30 and 40-47 are included in the rejection for being dependent of a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicants indicate claim 1 has been amended to contain R¹, R² and R³ each are an amino acid, x is an integer ≥ 0 , y is an integer ≥ 0 . The argument is not found persuasive because the new term does not clearly indicate which amino acid is used for R¹, R² and R³ and how many R¹, R² and R³ are included in the peptide, therefore, it is not clear what amino acid sequence the peptide would have.

10. Claim 4 recites the limitation "ACAA, Gly_p, Ala_q" In lines 3-5. There is insufficient antecedent basis for this limitation in the claim. R¹, R² or R³ is defined in claim 1 as being one amino acid, while R¹ is ACAA, Gly_p, or Ala_q is indicated in claim 4. See also claim 5.

11. Claim 6 is indefinite because of the use of the term “in a greater amount than”. The term “in a greater amount than” renders the claim indefinite, it is unclear in the claim how many more motifs of (A-C-B-A) than (A-B-C-A) are present in the formula.

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In response, applicants have amended the claim to use "in a greater amount than". The argument is not found persuasive because the claim does not clearly indicate how many more of (A-C-B-A) than (A-B-C-A).

12. Claim 8, for example, is indefinite because of the use of term "having SEQ ID NO:1". It is not clear how BP1 which consists of SEQ ID NO:1 as indicated in the specification (page 12, lines 19-20) can comprise SEQ ID NO:1 as recited in the claim. The term "having" is considered as "comprising". See also claims 9-12.

13. Claims 15, 24, 25 and 41 are indefinite because each claim recites a pharmaceutical composition comprising the same ingredients, it is not clear the claims differ from each other. The treatment of a specific disease state is an intended use which does not play any weight in the claim.

Conclusion

13. No claims are allowed.

Art of Record

The following two references appear to be the closest art to the claimed invention. Mee *et al.* (J. Peptide Res. 49, 89-102 (1997)) teach 15-residue antibacterial peptides such as CAM15, CAM111 and CAM 124, however these peptides only contain A-B-(A-C-B-A)₁ sequence. Tytler *et al.* (J. Biol. Chem. 268, 22112-22118 (1993)) teach an amphipathic helix peptide [R³, R⁴, R⁹, R¹⁴]18L (R-18L), but this peptide contains A-B-(A-B-C-A)₁ sequence.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

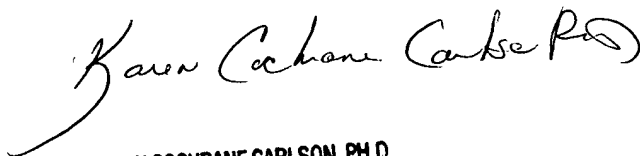
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

CMK

March 29, 2002


KAREN COCHRANE CARLSON, PH.D.
PRIMARY EXAMINER